UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/229,299	08/11/94	WEICHSELBAUM	

EXAMINER	
NEWELL, M	
ART UNIT	**PAPER NUMBER**
1804	5

18N2/0116

GARY J SERTICH
ARNOLD WHITE & DURKEE
PO BOX 4433
HOUSTON TX 77210

DATE MAILED: 01/16/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-36 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-36 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the invention, i.e. failing to provide an enabling disclosure.

The claimed invention is directed to gene therapy methods and compositions for the radioprotection and/or radiosensitizing of cells by the increase in transcription of a radioprotecting and/or radiosensitizing gene. The claimed invention is also directed to the gene therapy-mediated inhibition of tumor growth, in combination with radiotherapy (Claim 35). In specific embodiments, the radioprotective gene may encode tumor necrosis factor alpha (TNF-α), and the radiosensitizing genes may encode MnSOD (manganese superoxide dismutase), IL-1, IL-2, or TNF. The genes of the claimed invention may be delivered by any existing gene delivery system, although liposomes, adenovirus, and herpesvirus vectors are specifically claimed (Claims 8, 19). Additionally, the claimed invention specifies that gene

transcription be regulated by a constitutive promoter (Claims 1, 6, 14, 25, 28).

The claimed invention is directed to methods of gene therapy for cancer. The field of gene therapy, and more specifically cancer gene therapy, is undeveloped and unpredictable as is disclosed by Marshall ("Gene Therapy's Growing Pains", Science, August 25, 1995), and Brown ("Gene Therapy "Oversold" By Researchers, Journalists", Washington Post, December 8, 1995).

Marshall discloses that "so far there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1), and quotes NIH Director Harold Varmus that "despite the growing support for gene therapy", the field "remains at an early stage of development. While there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patients - or even in animal models" (page 1050, column 2). Marshall discloses that any encouraging results regarding the gene therapy treatment of cancer are at present anecdotal (page 1054, column 2). Brown discloses a December 1995 report of a panel of scientific advisers to NIH Director Harold Varmus, which concludes that "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol" ((page A22, column 1).

Both the Marshall and Brown references disclose a limitation of currently available gene transfer methods that is directly relevant to practice of the claimed invention: the lack of a gene delivery system capable of effective levels of gene transduction and expression in vivo. Blaese et al. reviews the state of the prior art in the field of vectors for cancer gene therapy. Blaese discloses the low rate of retroviral transduction of tumor cells (page 291, column 2), as well as possible disruption of cellular control mechanisms, induction of transformation in transformed cells, and recombination with endogenous viruses to produce replication competent retroviruses either in production of vectors or in the subjects themselves. Blaese also discloses that in vivo delivery of retroviral vectors is hampered by 1) the observation that expression of retrovirally-transferred cells sometimes diminishes with time, 2) evidence that intravenous delivery of retroviral vector to disseminated tumor is limited by the volume of viral supernatant required, and 3) the finding that conventional retroviral vectors are rapidly inactivated by primate complement (page 292, column 1).

Several working examples are presented in the specification, including 1) demonstration of the radiosensitizing effect of exogenously added TNF in cultured cell lines and human patients (Examples I-III), 2) the use of adenoviral, liposome, and herpesvirus vectors to transfer TNF into cultured cell lines and act synergistically with ionizing radiation to kill cultured

tumor cells, and 3) prophetic examples employing TIL cells to deliver TNF to a tumor site, with subsequent radiotherapy (Example XI), and the use of adenoviral-delivered TNF in conjunction with radiotherapy to treat human patients (Example X).

The working examples in the specification do not disclose 1) radioprotection of normal tissue by the TNF gene in cultured cells, animal models, or human beings, 2) vectors, gene transfer, and expression, or radioprotection by the MnSOD, IL-1, or IL-2 genes of the claimed invention, 3) demonstration of the synergistic effect of radiotherapy and a delivered radiosensitizing gene in any animal, including humans, and 4) demonstration of therapeutic benefit using any embodiment of the claimed invention in humans or an established animal model. In the absence of such working examples, and in light of the unpredictable and undeveloped nature of the field of cancer gene therapy as described in the above references, one of skill in the art would not accept on its face therapeutic radioprotection and/or radiosensitivity conferred upon any animal, including humans, by the vectors and methods of the claimed invention without undue experimentation and with a reasonable expectation of success.

In light of the quantity of experimentation necessary to make and use the invention, the amount of guidance and direction presented, consideration of the working examples, the nature of

the invention, the state of the prior art, the relative skill of those in that art, the degree of unpredictability of the art, and the breadth of the claims, the specification is not considered to adequately teach how to make and use the claimed invention.

Claims 1-36 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 8 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Both Claims 8 and 19 recite the transfection of cells by TIL (tumor infiltrating lymphocytes). This claim language is confusing in that TIL are not known in the art as a gene transfer vector and are not defined as such in the specification in any manner. Appropriate correction is requested.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102

of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-36 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 92/11033 in view of Neta et al. ("Radioprotection with Cytokines...", cited by applicant), and the applicant's specification.

The claimed invention is directed to gene therapy methods and compositions for the radioprotection and/or radiosensitizing of cells by the increase in transcription of a radioprotecting and/or radiosensitizing gene. The claimed invention is also directed to the gene therapy-mediated inhibition of tumor growth, in combination with radiotherapy.

WO 92/11033 discloses genetic constructs encoding tumor necrosis factor for the radiosensitizing of cells (including tumor cells), and the subsequent destruction of these cells by gene transfer and ionizing radiation. WO 92/11033 discloses that the genetic construct may be incorporated by electroporation, lipofection, or retroviral methodology (page 6) - "any method

which incorporates the construct without inhibiting its desired expression and control over that expression by radiation" (lines 18-23). On page 8, the reference discloses the desirability of LAK cells to target the constructs to tumor regions.

The reference differs from the claimed invention in that the reference specifies a radiation-responsive promoter rather than the constitutive promoter of the claimed invention, the reference does not specifically disclose the use of gene transfer vectors for radioprotection, and does not specifically disclose herpes virus and adenovirus as vectors for transfer of radiosensitizing genes.

Neta et al. provides the motivation to use IL-1 or TNF as radioprotecting genes, which could be substituted into the genetic constructs of WO 92/11033 by one skilled in the art to limit radiation damage to normal tissues.

The specification discloses that a variety of vector systems have been demonstrated to deliver genes in vivo, and that a number of constitutive promoters exist in the art for the constitutive expression of a therapeutic gene product. One skilled in the art would be able to select appropriate gene transfer vectors and regulatory elements in accordance with those known in the art to transfer the radiosensitizing genes disclosed by WO 92/11033, and the radioprotecting genes disclosed by Neta.

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfer

radioprotecting and/or radiosensitizing genes to alternately protect normal tissues or synergistically kill tumor tissue during radiotherapy, based on the combination of WO 92/11033 and Neta et al. It would be further obvious to use known gene transfer vectors (such as adenovirus) and known regulatory elements (such as constitutive promoters) based on the disclosure of WO 92/11033 regarding gene transfer vectors, and the desire to express radioprotecting and/or radiosensitizing genes in a constitutive manner before, during and after radiotherapy.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Newell whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday to Friday from 8:30 AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on (703) 308-3153 . The fax phone number for this Group is (703)308-4312.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196.

Michael Newell

January 7, 1995

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800